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DAMINOZIDE

SPECIAL REVIEW

TECHNICAL SUPPORT DOCUMENT -

PRELIMINARY DETERMINATION TO CANCEL THE

FOOD USES OF DAMINOZIDE

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Office of Pesticide Programs

Office of Pesticides and Toxic Substances

United States Environmental Protection Agency

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EXECUTIVE SUMMARY

This document contains the Environmental Protection Agency's (EPA's) evaluation of the risks and benefits of the plant growth regulator daminozide and the basis for the Agency's proposed cancellation of the food uses of daminozide.

Daminozide is the accepted, common name for butanedioic acid mono (2,2-dimethylhydrazide). Daminozide (trade name Alar®) was first registered in 1963 by the Uniroyal Chemical Company, Inc., for use on potted chrysanthemums. The first food use of daminozide was registered in 1968 for use on apples. Daminozide is currently registered for use as a plant growth regulator to control vegetative and reproductive growth of orchard crops including apples, cherries, nectarines, peaches, and pears. Daminozide affects flower bud initiation, fruit set and maturity, fruit firmness and coloring, preharvest fruit drop and the market quality of fruit at harvest and during storage. Daminozide is also used to enhance shorter and more erect peanut vines, suppress growth of tomatoes, and modify the stem length and shape of ornamental plants. In 1985, it was estimated that 49-77 percent of the total daminozide usage was on apples, approximately 26 percent of daminozide usage was on peanuts, and 5 percent was on ornamentals. Since 1985, daminozide use on both apples and peanuts has decreased significantly while the non-food uses have remained steady.

On July 18, 1984, EPA issued a Notice of Initiation of a Special Review (which included a Position Document 1 or PD 1) of pesticide products containing daminozide (49 FR 29186). This action was based on the Agency finding that pesticide products containing daminozide met the risk criterion relating to oncogenicity formerly at 40 CFR 162.11(a)(3)(ii)(A) and now found at 40 CFR 154.7(a)(2)(i). At that time, the relevant portion of 40 CFR 162.11 provided that a Special Review shall be conducted if the use of a pesticide "induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure...." Specifically, available data indicated that administration of daminozide and its degradate and metabolite, unsymmetrical dimethylhydrazine (UDMH), to laboratory animals resulted in statistically and biologically significant oncogenic responses at multiple organ sites in multiple species and strains of animals. UDMH was believed to be a very potent animal carcinogen and mutagen.

In September 1985, the Agency developed a Draft Notice of Intent to Cancel and a Draft PD 2/3/4 in which cancellation of the food uses of daminozide on the basis of cancer dietary risk

was proposed. The Scientific Advisory Panel (SAP), reviewed the Draft Cancellation Notice and Draft PD 2/3/4 and concluded that the studies relied on by the Agency did not support quantitative cancer risk assessment. The Panel, which was established by Congress to provide scientific review of EPA pesticide actions, believed the data raised concern, but that the studies used by the Agency were sufficiently limited that they were inappropriate for risk assessment.

After consideration of the comments made by the SAP, the Agency decided to postpone any further activity on the cancellation action at that time. However, the Agency did decide to require development of additional data to fully characterize the oncogenic risk of daminozide and UDMH before making any further regulatory decisions. In February 1986, the Agency imposed extensive data requirements on daminozide registrants under section 3(c)(2)(B) of FIFRA. The required data included additional oncogenicity studies, mutagenicity data, plant and animal metabolism studies, livestock feeding data, crop field trials, degradation in food data, storage stability information, market basket surveys, and development of refined, more sensitive detection methodologies.

In the interim period while data were being generated, the Agency determined that certain changes to daminozide registrations intended to reduce human exposure were appropriate. These included: reduced label application rates for apples and limitation of the use on grapes to Concord grapes (not for use as raisins). In addition, the Agency established a lower apple tolerance with a specific expiration date.

By the end of December 1988, much of the required data had been received and reviewed by the Agency. As a result of the review of these data, in particular a 12-month interim sacrifice report of a UDMH oncogenicity study in mice, the Agency has preliminarily determined that dietary exposure to UDMH represents a significant carcinogenic risk which outweighs the benefits of use of daminozide on food crops and therefore warrants the cancellation of the food uses of daminozide. The carcinogenic risk posed by non-dietary exposure to daminozide and UDMH do not outweigh the benefits and are not significant enough to take cancellation action. Therefore, the Agency is proposing that non-food uses be continued without modification of the terms and conditions of registrations.

The Agency has recently evaluated the new Uniroyal data in conjunction with the previously considered (historical) data on daminozide and UDMH in a weight-of-the-evidence determination. Based on this evaluation both daminozide and UDMH were classified

as B2 chemicals, probable human carcinogens. In both the historical studies (NCI 1978; Toth 1977), judged inadequate for risk assessment by the SAP in 1985 and the new Uniroyal studies, daminozide produced vascular and lung tumors in mice. In the more recent Uniroyal mouse study, daminozide showed a statistically significant increase in hemangiomas/ hemangiosarcomas with increasing dose (Cochran Armitage trend analysis), but not by pairwise comparison (Fisher's exact test - a statistical comparison of control and treated animals). A dose-related trend for lung tumors was also seen in male mice. The Agency believes the new data supported by the occurrence of similar tumors in the historical data are sufficient to classify daminozide as a probable human carcinogen. However, the Agency also believes the oncogenic response seen in the daminozide studies is likely caused by the presence of UDMH in the test material and/or metabolic conversion to UDMH.

Vascular and lung tumors seen in the historical UDMH data were also seen in the one-year interim sacrifice in mice from the new Uniroyal study at 80 and 40 ppm. The increase in vascular tumors at 80 ppm was statistically significant by pairwise comparison and trend analysis. UDMH has produced a clear oncogenic response in mice at the highest dose tested and the Agency anticipates that an increase in vascular tumors will also be seen at the lower dose at terminal sacrifice (the 40 ppm dose showed one hemangioma in both a male and female mouse at the one year interim sacrifice).

Neither the Uniroyal rat studies in daminozide (completed) and UDMH (one-year interim sacrifice) or the historical rat data produced treatment related lung or vascular tumors in feeding studies.

The Agency has used data from a 1986 market basket survey, recent crop field trial data, and recently conducted animal feeding studies to estimate exposure for both daminozide and UDMH. From the interim sacrifice report of the UDMH mouse cancer study, the Agency calculated an interim carcinogenic potency factor based on the incidence of hemangiosarcomas (malignant vascular tumors) and combined hemangiomas/hemangiosarcomas of the liver. Based upon this information, the Agency has estimated the lifetime risk of cancer for the general population due to dietary exposure to UDMH to be 4×10^{-5} (5×10^{-5} if an estimate of metabolic conversion of daminozide to UDMH in the gut is considered). (The lifetime risk to the general population [4×10^{-5}] is somewhat lower than the risk cited in the Apple Tolerance Extension document of January 31, 1989 [54 FR 6392] because of a slight overestimate of dietary exposure made in the tolerance document.) The Agency is particularly concerned that a disproportionate share of the lifetime risk occurs from childhood

exposure because of the high ratio of food intake per unit bodyweight and the relatively high proportion of a child's diet that is composed of foods which may contain daminozide and UDMH residues. The annual lifetime risk to non-nursing infants (0 to 1 year of age), the highest exposure group, from one year exposure to UDMH is estimated to be approximately 5×10^{-5} (6×10^{-5} if 1 percent metabolic conversion is assumed). The Agency has sought the advice of the National Academy of Science (NAS) as to whether relatively high exposure during infancy and childhood make a person more susceptible to cancer later in life.

The benefits from daminozide use have been assessed in terms of economic impacts which would result if the registered uses of daminozide were cancelled. In assessing benefits, the Agency considered uage information from 1985 and 1988. The Agency concluded the overall impacts from cancellation of daminozide on food uses would be insignificant to minor. Although there are alternatives for some of daminozide's uses, no one alternative chemical provides all the benefits of daminozide. For food uses, the greatest anticipated annual impacts would be in apple production. Estimates of the economic impact on the apple industry are based on 10 percent of the crop treated. Earlier estimates made in conjunction with the apple tolerance extension document of January 31, 1989, referenced a 4 to 8 percent annual crop treatment. The higher estimate (5 to 10 percent) in this document is a result of additional and more in-depth information gathered in the last two months.

Based on 1988 usage data, impacts on the apple use, in terms of net social cost for the whole of society, could range from $18 - 81 million with the most likely impact approaching the lower end of this range. Growers of Stayman and McIntosh varieties would suffer the greatest individual impact. For other food uses, the annual impacts are anticipated to be approximately $1.5 - 5.5 million for peaches, approximately $260,000 for peanuts, and negligible impacts for nectarines, cherries, grapes, and pears. The Agency needs additional information regarding the benefits of daminozide use on tomato transplants and is requesting this information in this document.

The Agency considered a number of options to further reduce dietary exposure and thus reduce carcinogenic risk. In particular, limiting use to certain crops and varieties was considered. None of the considered options was found to reduce the cancer risk such that benefits outweighed risks. Therefore, since the risks of continued use outweigh the benefits, EPA is proposing cancellation of all food uses.

The Agency also considered an emergency suspension of daminozide use on food crops. Although EPA believes that the available data are a cause for concern, the level of risk during the time necessary to complete a cancellation action is not unreasonably high. Also, exposure is expected to decrease as a result of declining use which will further reduce risk.

The Agency has also examined the risks and benefits of non-dietary exposure. The Agency estimated that the greatest individual lifetime cancer risks posed by non-dietary exposure to UDMH from use on greenhouse ornamentals is 1×10^{-6}. In addition, the Agency believes that annual grower and consumer losses (as high as $4.7 million in an industry with an annual wholesale value of $78.5 to $104.5 million) would be substantial if the uses of daminozide on ornamentals and bedding plants were cancelled. In this case, the Agency believes that the benefits outweigh the risks for non-dietary use of daminozide on ornamentals and bedding plants. The Agency is proposing that all registrations for use on ornamentals and bedding plants be retained without modifications to the label.

The Agency will also be proposing in the near future the revocation of daminozide tolerances for all raw agricultural commodities as well as the daminozide food and feed additive regulations for processed commodities. No separate tolerances or food and feed additive regulations have been established for UDMH. As noted above, the Agency established a lower tolerance for daminozide on apples with an expiration date while data were being generated. On January 31, 1989 (54 FR 6392; February 10, 1989), the apple tolerance was extended for an additional 18 months to allow the Agency time to complete the Special Review of daminozide.